REMARKS

Claims 1-58 constitute the pending claims in the present application. Applicants cancel without prejudice, claims 13-39. Claims 8-12 and 40-50 are withdrawn from consideration as being directed to a non-elected invention. Applicants will cancel such claims upon indication of allowable subject matter. Applicants add new claims 51-58. Support for the subject matter of these claims, as well as for the amendments to claims 1 and 2, is found throughout the specification. No new matter has been entered. Explicit support for the subject matter of the pending claims is found, for example, on page 4, lines 30-31; page 9, lines 30-35; page 10, lines 1-8; page 16, lines 32-34; and page 17, lines 20-24. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note that the amendment to the specification to correct the obvious typographical error when referring to the sequence listing has been entered. Applicants note that the pending claims are directed to compositions comprising PYY agonists comprising polypeptides. In certain embodiments, such polypeptides are encodable by a nucleic acid represented in SEQ ID NO: 1, or by a nucleic acid that hybridizes under stringent conditions to a nucleic acid represented in SEQ ID NO: 1. Given that the pending claims are all directed to PYY agonists comprising polypeptides, Applicants contend that the claims encompass a single invention consistent with the previously elected invention.

Applicants note for the record that the correction to the sequence listing was made to correct an obvious typographical error in the specification by which the PYY amino acid sequence was referred to as SEQ ID NO: 1 (a nucleic acid sequence).

2. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to practice the claimed invention. Applicants traverse this rejection and maintain that it is moot in light of the amended claims.

The basis of the rejection appears to be two-fold. First, the Examiner alleges that the specification fails to enable methods of promoting the growth or reducing the degeneration of cells. Second, the Examiner alleges that the specification fails "to teach how to make PYY

fragments or PYY agonists that would maintain the activity of promoting growth and reducing degeneration of pancreatic cells." (previous Office Action, page 4, 2nd complete paragraph).

In response to the first grounds of rejection, Applicants contend that the application, as well as the art at the time of filing, support the enablement of claims directed to methods of promoting the growth and reducing the degeneration of cells. Applicants direct the Examiner's attention to the teachings of Voisin et al., 1993 (enclosed herewith as Exhibit 1). The results provided in Voisin et al. demonstrated both the expression of PYY receptors on proximal kidney tubule cells, and the use of exogenously supplied PYY to promote the growth of those cells. Specifically, Voisin et al. observed a PYY-dependent increase in cell growth of 17-26% (see, Abstract).

The teachings of Voisin et al. demonstrate that the promotion of cell growth in cells expressing PYY receptors is one of the functions of PYY. Although Voisin et al. is silent as to the expression or function of PYY in pancreatic cells, the application as filed provides several working examples demonstrating that PYY exerts a number of effects on pancreatic cells. Accordingly, absent evidence to the contrary, Applicants contend that no reasonable basis exists to question the enablement of the claimed invention.

MPEP 2164.04 outlines the criteria for evaluating enablement. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The reasoning outlined in MPEP 2164.04 is well supported by the Court which stated that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the

contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out certain embodiments of Applicants' invention. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Applicants' amendments to the claims are fully supported by the specification (see, for example, page 4, lines 30-31; page 9, lines 30-35; page 10, lines 1-8; page 16, lines 32-34; page 17, lines 20-24). Additionally, although not a requisite for compliance with 35 U.S.C. 112, first paragraph, the specification provides working examples which demonstrate the successful use of PYY in the presently claimed methods (see, Examples 3-6 and 10). Accordingly, Applicants request reconsideration and withdrawal of this rejection.

In response to the second grounds of rejection, Applicants contend that the specification and the art provide extensive guidance as to the making and testing of PYY variants and fragments. By way of just a few examples, Applicants cite the teachings of Liu et al., 1996, Litvak et al., 1999, and Balasubramaniam et al., 2000 to demonstrate the broader class of both peptide and non-peptide PYY agonists known in the art (enclosed herewith as Exhibits 2-4). Additionally, column 3 of U.S. Patent 5,574,010, incorporated by reference in the specification at page 23, line 27, points out a number of other references relating to compounds that fall within the scope of the term 'PYY agonists'. The art at the time of filing thus included a panoply of 'PYY agonists' as this term is used in the specification and pending claims. Furthermore, one of ordinary skill in the art using assays described in these references could have identified any number of additional PYY agonists using only routine experimentation. Applicants respectfully remind the Examiner that "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01(a).

Applicants contend that the application, as well as the art at the time of filing, supports the enablement of claims which employ a broad range of PYY agonists including both peptide and non-peptide agonists. Furthermore, the specification provides a number of cell and animal-

based assays in which one could readily evaluate the relative efficacy of other PYY agonists using only routine experimentation. Such PYY agonists are described not only with reference to sequence and structural information, but also with reference to their function. Accordingly, one of skill in the art can readily recognize and appreciate the PYY agonists for use in the claimed methods.

The Examiner has cited Wells to support the notion that because changes in primary sequence can affect the function of a protein or peptide, Applicants are not entitled to claims directed to the use of a broader range of peptide agonists. In response to this argument, Applicants raise the following two points. First, even if the claims encompass certain inoperative embodiments, that does not undermine the enablement of the operative subject matter. In accordance with MPEP 2164.08(b), "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." This standard has been upheld in the courts, and permits a claim to encompass a finite number of inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application without undue experimentation. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976).

Second, Applicants point out that the Wells reference relied upon by the Examiner was published in 1990. Since that time, there has been a veritable explosion in the art of combinatorial chemistry which readily allows the making and testing of polypeptide variants without undue experimentation. Thus, even if one agrees that small differences in polypeptide sequence can affect the function of a protein or peptide, this point is immaterial in assessing the enablement of the claimed methods. Rather, the important consideration in determining whether Applicants have enabled the use of PYY variants in the subject methods is whether one of skill in the art could readily make and test polypeptide variants using the teachings of the specification and the state of the art, without undue experimentation, in order to select PYY variants for use in the subject methods. Applicants contend that this burden has been met.

The specification provides a detailed description of methods of making and testing variants using combinatorial mutagenesis (page 23, line 8-page 24, line 27). Furthermore, the specification provides several cell based and animal models in which PYY variants can be tested for efficacy in the subject methods. Given the extensive guidance provided in the specification, as well as the high level of skill in the art, Applicants contend that one of skill in the art can readily make and test PYY variants to identify variants which meet the structural and functional limitations recited in the claims without undue experimentation.

Additionally however, Applicants are not merely relying upon the ability of one of skill in the art to make and test peptide variants in order to select variants for use in the methods of the present invention. Applicants reiterate the arguments of record, and remind the Examiner that several PYY variants had been identified and the ability of these variants to mimic one or more functions of PYY had been demonstrated. Accordingly, these examples demonstrate that not only **could** one of skill in the art make and test variants to identify those variants with particular functional attributes, but one of skill in the art **did** make and test variants to identify variants with particular attributes.

In light of Applicants' amendments and arguments, and in light of the criteria for evaluating enablement outlined in detail in MPEP 2164.01, Applicants contend that the claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection is respectfully requested.

3. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to be described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants traverse this rejection and maintain that it is moot in light of the amended claims.

As discussed in detail in section 2 above, Applicants contend that claims directed to the use of the claimed PYY agonists in the subject methods are enabled throughout their scope. Applicants further contend that the specification provides an adequate description for a wide range of PYY agonists including peptide and non-peptide agonists. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out the claimed subject matter. Applicants'

amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. The presently claimed PYY polypeptides for use in the subject methods are adequately described in the specification and in the art using both structural and functional features, and accordingly, one of skill in the art can readily envision that which is claimed.

In summary, Applicants have described the genus of PYY agonists for use in the claimed methods using both structural and functional criteria, and thus one of skill in the art can readily envision the claimed subject matter. Reconsideration and withdrawal of this rejection are respectfully requested.

4. Claims 1-2 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Bertrand et al. Applicants traverse this rejection and contend that it is moot in light of the amended claims.

Bertrand et al. fail to satisfy the criteria for anticipating Applicants' invention. Both the MPEP and the Federal Circuit support Applicants' contention that in order to anticipate or render obvious the claimed invention, the cited art must teach all the limitations of the claimed subject matter (MPEP 2131). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegall Bros. v. Union Oil Company of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the .... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ3d 1913, 1920 (Fed. Cir. 1989). Bertrand et al. fail to teach the particular combination of elements of the pending claims (enclosed herewith as Exhibit 5). Specifically, Bertrand et al. fail to teach that PYY promotes the glucose-responsiveness of pancreatic cells. In fact, Bertrand et al. explicitly state that, at the concentrations utilized in their studies, PYY either inhibited or had no effect on insulin secretion in response to glucose (see Abstract).

Bertrand et al. fail to teach or suggest that PYY can be used to promote or enhance glucose responsiveness in pancreatic cells. In fact, in experiments conducted over a 100-fold range of PYY concentrations, Bertrand et al. achieved a result **opposite** to that required by the pending claims. Accordingly, not only does Bertrand et al. fail to teach the presently claimed

methods, Bertrand et al. **teach away** from the effective use of PYY in the presently claimed methods. In light of Applicants' amendments and arguments, reconsideration and withdrawal of this rejection are respectfully requested.

5. Applicants note for the record that claims 3-6 have been voluntarily amended for the purpose of clarity, and Applicants' amendments to these claims do not narrow their scope. One of skill in the art readily appreciates that various tissues in the body are composed of cells. Therefore, in the context of the presently claimed invention, methods which effect the glucose responsiveness of pancreatic tissue necessarily effect the glucose responsiveness of the cells which comprise that tissue.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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